Risk of Suicide Attempts Among Adolescents and Young Adults With Autism Spectrum Disorder: A Nationwide Longitudinal Follow-Up Study

Mu-Hong Chen, MD[a,b,‡]; Tai-Long Pan, PhD[c,d,e,‡]; Wen-Hsuan Lan, MD[a,f]; Ju-Wei Hsu, MD[a,b]; Kai-Lin Huang, MD[a,b]; Tung-Ping Su, MD[a,b]; Cheng-Ta Li, MD, PhD[a,b]; Wei-Chen Lin, MD[a,b]; Han-Ting Wei, MD[a,g]; Tzeng-Ji Chen, MD, PhD[h,i]; and Ya-Mei Bai, MD, PhD[a,b,*]

ABSTRACT

Background: Previous studies reported a high prevalence of depression among patients with autism spectrum disorder (ASD) and suggested a relationship between ASD and suicidality. However, whether ASD independently increases the risk of attempted suicide regardless of depression has not been determined.

Methods: Using the Taiwan National Health Insurance Research Database, 5,618 adolescents aged 12–17 years and young adults aged 18–29 years with ASD (*ICD-9-CM* code: 299) and 22,472 age- and sex-matched controls were enrolled between 2001 and 2009 and followed to the end of 2011. Any suicide attempt was identified during the follow-up period.

Results: Patients with ASD had a higher incidence of suicide attempts (3.9% vs 0.7%, $P < .001$) than did those without ASD. Both adolescents (HR = 5.79; 95% CI, 3.98–8.41) and young adults (HR = 5.38; 95% CI, 3.58–8.06) with ASD were more likely to attempt suicide in later life after adjusting for demographic data and psychiatric comorbidities. Sensitivity analyses after excluding the first year (HR = 4.52; 95% CI, 3.39–6.03) or first 3 years (HR = 3.36; 95% CI, 2.40–4.70) of observation showed consistent findings.

Conclusions: Patients with ASD had an increased risk of suicide attempts compared with those without ASD. ASD was an independent risk factor of attempted suicide. Further studies are needed to clarify the underlying pathophysiology between ASD and suicidality and to elucidate whether prompt intervention for ASD may reduce this risk.

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[a]Department of Psychiatry, Taipei Veterans General Hospital, Taipei, Taiwan
[b]Department of Psychiatry, College of Medicine, National Yang-Ming University, Taipei, Taiwan
[c]School of Traditional Chinese Medicine, Chang Gung University, Taoyuan, Taiwan
[d]Liver Research Center, Chang Gung Memorial Hospital, Taoyuan, Taiwan
[e]Department of Medical Research, China Medical University Hospital, China Medical University, Taichung, Taiwan
[f]Division of Psychiatry, Taipei Municipal Gan-Dau Hospital, Taipei, Taiwan
[g]Division of Psychiatry, Kunming Branch, Taipei City Hospital, Taipei, Taiwan
[h]Department of Family Medicine, Taipei Veterans General Hospital, Taipei, Taiwan
[i]Institute of Hospital and Health Care Administration, National Yang-Ming University, Taipei, Taiwan
‡Contributed equally.
*Corresponding author: Ya-Mei Bai, MD, PhD, Department of Psychiatry, No. 201, Shih-Pai Rd, Sec. 2, 11217, Taipei, Taiwan (ymbi@mail2000.com.tw).

Autism spectrum disorder (ASD) is a neurodevelopmental disorder typified by deficits and impairments in social cognition, interpersonal interaction, and reciprocal communication as well as by repetitive behaviors and restricted interests.[1–3] Population reports have shown a consistent and significant increase in ASD prevalence worldwide (approximately 0.6%–0.7%); the latest large-scale studies estimated a 1%–2% increase.[1–3] Males are 2 to 3 times more likely to be affected by ASD than are females, indicating the crucial impact of sex-linked factors at the genetic, endocrine, epigenetic, and environmental levels in the pathophysiology of ASD.[1–3] However, the precise etiology of ASD remains unclear.

Several recent studies have suggested a potential relationship between ASD and suicidality.[4–10] A retrospective study composed of 18 adults who had a history of suicide attempts and 32 adults who did not demonstrated that those who attempted suicide were more likely to have a history of depression and self-reported more severe ASD symptomatology.[6] Storch et al assessed the presence of suicidal ideation and behaviors in 102 youths with ASD through the Anxiety Disorders Interview Schedule and reported that approximately 11% of the youths displayed suicidal ideation and behaviors, which were associated with the presence of depression and traumatic experiences.[9] In a clinical cohort study in which 374 adults with ASD completed a self-report questionnaire recording lifetime experiences of depression, suicidal ideation, and suicide plans or attempts. Cassidy et al found that patients with ASD had an increased likelihood of the lifetime experience of suicidal ideation compared with people from a general United Kingdom population sample (odds ratio [OR] = 9.6; 95% confidence interval [CI], 7.6–11.9]) and furthermore revealed that patients who reported suicide plans or attempts exhibited significantly higher Autism Spectrum Quotient scores than people who did not.[4] However, the aforementioned studies had several limitations including a small sample of patients with ASD; the use of a self-report questionnaire rather than a medical document providing evidence of suicidality, especially suicide attempts, resulting in a lower validity of suicidality measurement; and the application of a retrospective study design instead of a longitudinal follow-up study design, causing a higher recall bias in suicidality measurement. In addition, whether ASD has an independent effect on the risk of suicidality remains unclear according to previous studies.

In our study, using the Taiwan National Health Insurance Research Database with a large sample size and a longitudinal

Clinical Points

- Adolescents and young adults with ASD exhibited an elevated likelihood of attempting suicide in later life compared with those without ASD.
- Suicide-related symptoms, psychopathology, and psychiatric comorbidities, including depression and alcohol and substance use disorders, should be more closely monitored in clinical practice among patients with ASD.

Table 1. Demographic Data and Incidence of Suicide Attempts Among Adolescents and Young Adults With ASD and Controls

	Adolescents and Young Adults With ASD (n = 5,618)	Controls (n = 22,472)	*P* Value
Age at enrollment, mean (SD), y	17.20 (4.58)	17.20 (4.58)	
Sex, n (%)			
Male	4,393 (78.2)	17,572 (78.2)	
Female	1,225 (21.8)	4,900 (21.8)	
Incidence of cases with any suicide attempt, n (%)	219 (3.9%)	154 (0.7)	< .001
Age at first suicide attempt, mean (SD), y	22.23 (5.61)	25.06 (5.46)	< .001
Duration between enrollment and the first suicide attempt, mean (SD), y	3.57 (2.63)	6.00 (2.58)	< .001
Psychiatric comorbidities, n (%)			
ADHD	1,423 (25.3)	259 (1.2)	< .001
Disruptive behavior disorders	370 (6.6)	41 (0.2)	< .001
Intelligence disability	2,404 (42.8)	151 (0.7)	< .001
Anxiety disorders	632 (11.2)	94 (0.4)	< .001
Unipolar depression	898 (16.0)	373 (1.7)	< .001
Bipolar disorder	473 (8.4)	73 (0.3)	< .001
Alcohol use disorder	65 (1.2)	214 (1.0)	.174
Substance use disorder	85 (1.5)	346 (1.5)	.947
Level of urbanization, n (%)			< .001
1 (most urbanized)	1,048 (18.7)	6,925 (30.8)	
2	1,709 (30.4)	6,882 (30.6)	
3	535 (9.5)	4,230 (18.8)	
4	485 (8.6)	2,942 (13.1)	
5 (most rural)	1,841 (32.8)	1,493 (6.6)	
Income-related insured amount			< .001
≤ 15,840 NTD/mo	4,860 (86.5)	13,059 (58.1)	
15,841–25,000 NTD/mo	694 (12.4)	6,009 (26.7)	
≥ 25,001 NTD/mo	64 (1.1)	3,404 (15.1)	

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, ASD = autism spectrum disorder, SD = standard deviation.

follow-up study design, we investigated the risk of suicide attempts among adolescents and young adults with ASD and clarified whether ASD increased the risk of attempted suicide independent of depression. We hypothesized that patients with ASD had an elevated likelihood of attempting suicide in later life after adjusting for psychiatric comorbidities, including depression.

METHODS

Data Source

Taiwan's National Health Insurance (NHI), a mandatory universal health insurance program, was implemented in 1995 and offers comprehensive medical care coverage to all Taiwanese residents. The National Health Research Institute (NHRI) is in charge of the entire insurance claims database, namely the National Health Insurance Research Database (NHIRD), which consists of health care data from > 97% of the entire Taiwan population (http://www.nhi.gov.tw/). The NHRI audits and releases the NHIRD for scientific and study purposes. Individual medical records included in the NHIRD are anonymous to protect patient privacy. Comprehensive information on insured individuals is included in the database, including demographic data, dates of clinical visits, disease diagnoses, and medical interventions. The diagnostic codes used were based on the *International Classification of Diseases*, Ninth Revision, Clinical Modification (*ICD-9-CM*). The NHIRD has been used extensively in many epidemiologic studies in Taiwan.[11–14]

Inclusion Criteria for Adolescents and Young Adults With ASD and the Control Group

Adolescents aged between 12 and 17 years and young adults aged between 18 and 29 years who were diagnosed with ASD (*ICD-9-CM* code: 299, pervasive developmental disorders) by board-certified psychiatrists based on clinical judgment and diagnostic interviews between January 1, 2001, and December 31, 2009, and who had no history of suicide attempts before enrollment, were included as the ASD cohort. The time of ASD diagnosis was defined as the time of enrollment. The age-, sex-, and time of enrollment–matched (1:4) control cohort was randomly identified after eliminating the study individuals, those who had been given a diagnosis of ASD at any time, and those with suicide attempts before enrollment. Any suicide attempt coded by emergency room physicians, psychiatrists, internal medicine physicians, and surgeons was identified during the follow-up period (from enrollment to December 31, 2011, or to death). Comorbid psychiatric diagnoses, including attention-deficit/hyperactivity disorder (ADHD), disruptive behavior disorders, intelligence disability, unipolar depression, bipolar disorder, anxiety disorders, alcohol use disorder, and substance use disorder, were made by board-certified psychiatrists on the basis of their clinical judgment and diagnostic interviews and assessed as the confounding factors in our study. All psychiatric diagnoses were made at least twice by board-certified psychiatrists. Level of urbanization (levels 1–5; level 1: most urbanized region, level 5: least urbanized region) was also assessed for our study.[15] The Taipei Veterans General Hospital institutional review board approved this study.

Statistical Analysis

For between-group comparisons, the independent *t* test was used for continuous variables and Pearson χ^2 test for nominal

variables, where appropriate. Four Cox regression models were performed to calculate the hazard ratio (HR) with a 95% confidence interval (CI) of suicide attempts among adolescents and young adults with ASD and the control group. Model 1 was adjusted for demographic data; model 2 was adjusted for demographic data, ADHD, disruptive behavior disorders, and intelligence disability; model 3 additionally adjusted for mood disorders (anxiety disorders, unipolar depression, bipolar disorder); and model 4 further adjusted for alcohol and substance use disorder. Sensitivity analyses were performed to investigate the above associations after excluding the first year or first 3 years of observation. We also performed subanalyses of the risk of suicide attempts with ASD stratified by sex and age groups: adolescents (< 18 years) and young adults (18–29 years). A 2-tailed *P* value of less than .05 was considered statistically significant. All data processing and statistical analyses were performed with Statistical Package for Social Science (SPSS) version 17 software (SPSS Inc, Chicago, Illinois) and Statistical Analysis Software (SAS) version 9.1 (SAS Institute, Cary, North Carolina).

RESULTS

In all, 5,618 adolescents and young adults aged 17.20 ± 4.58 years and 22,472 age- and sex-matched controls were enrolled in our study, with a male predominance (78.2%). One hundred thirteen ASD patients with history of suicide attempts before enrollment were excluded in the ASD cohort. The ASD cohort exhibited an increased incidence of suicide attempts (3.9% vs 0.7%, $P < .001$) and a shorter duration between the enrollment and the first suicide attempt (3.57 ± 2.63 years vs 6.00 ± 2.58 years, $P < .001$) compared with the control group (Table 1). Adolescents and young adults with ASD had a higher prevalence of ADHD (25.3% vs 1.3%, $P < .001$), disruptive behavior disorders (6.6% vs 0.2%, $P < .001$), intelligence disability (42.8% vs 0.7%, $P < .001$), anxiety disorders (11.2% vs 0.4%, $P < .001$), unipolar depression (16.0% vs 1.7%, $P < .001$), and bipolar disorder (8.4% vs 0.3%, $P < .001$) than the controls (Table 1). Patients with ASD resided in less urbanized regions ($P < .001$) and had a lower income-related insured amount ($P < .001$).

Kaplan-Meier survival analysis with a log-rank test demonstrated that adolescents and young adults with ASD had a higher likelihood of suicide attempts ($P < .001$) than the control group (Figure 1). The Cox regression model showed that ASD increased the risk of attempted suicide (HR = 6.07; 95% CI, 4.64–7.93) after adjusting for demographic data and psychiatric comorbidities (ADHD, disruptive behavior disorders, intelligence disability, mood disorders, and alcohol and substance use disorders) (Table 2). Subanalyses stratified by sex and age group further revealed that both males (HR = 6.55; 95% CI, 4.78–8.98) and females (HR = 4.80; 95%

Figure 1. Survival Curve for Developing Any Suicide Attempt Among Adolescents and Young Adults With Autism Spectrum Disorder (ASD) and Controls

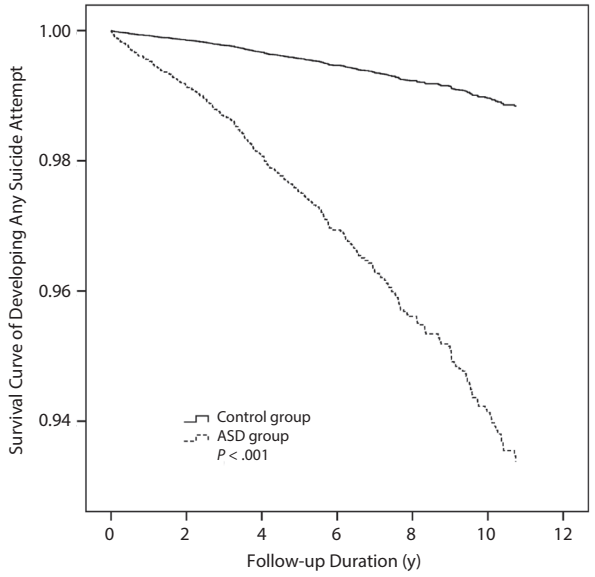

Table 2. Cox Regression Analyses of the Risk of Subsequent Suicide Attempts Among Adolescents and Young Adults With ASD and Controls[a]

	Model 1[b]		Model 2[c]		Model 3[d]		Model 4[e]	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
ASD (presence vs absence)	**5.83**	**4.62–7.30**	**6.31**	**4.87–8.17**	**6.01**	**4.60–7.85**	**6.07**	**4.64–7.93**
Psychiatric comorbidities (presence vs absence)								
ADHD			0.76	0.53–1.10	0.76	0.53–1.10	0.77	0.53–1.10
Disruptive behavior disorders			1.12	0.65–1.94	1.07	0.62–1.86	1.04	0.60–1.81
Intelligence disability			0.90	0.69–1.17	0.89	0.68–1.17	0.89	0.68–1.17
Anxiety disorders					0.80	0.51–1.26	0.81	0.52–1.27
Unipolar depression					**1.47**	**1.07–2.03**	**1.41**	**1.03–1.95**
Bipolar disorder					1.06	0.85–1.31	1.03	0.83–1.28
Alcohol use disorder							**2.00**	**1.09–3.70**
Substance use disorder							**2.01**	**1.18–3.42**

[a]Bold type indicates statistical significance.
[b]Model 1: adjusted for demographic data.
[c]Model 2: adjusted for demographic data, ADHD, disruptive behavior disorders, and intelligence disability.
[d]Model 3: adjusted for demographic data, ADHD, disruptive behavior disorders, intelligence disability, and mood disorders.
[e]Model 4: adjusted for demographic data, ADHD, disruptive behavior disorders, intelligence disability, mood disorders, and alcohol and substance use disorders.
Abbreviations: ADHD = attention-deficit hyperactivity disorder, ASD = autism spectrum disorder, CI = confidence interval, HR = hazard ratio.

Table 3. Cox Regression Analyses of the Risk of Subsequent Suicide Attempts Among Adolescents and Young Adults With ASD and Controls, Stratified by Age and Sex[a,b]

	Adolescents <18 y HR (95% CI)	Young Adults 18–29 y HR (95% CI)	Males HR (95% CI)	Females HR (95% CI)	Total HR (95% CI)
ASD					
Absence	1	1	1	1	1
Presence	**5.79 (3.98–8.41)**	**5.38 (3.58–8.06)**	**6.55 (4.78–8.98)**	**4.80 (2.86–8.06)**	**6.07 (4.64–7.93)**
Psychiatric comorbidities (presence vs absence)					
ADHD	0.86 (0.56–1.30)	0.85 (0.34–2.10)	0.83 (0.53–1.23)	0.57 (0.20–1.58)	0.77 (0.53–1.10)
Disruptive behavior disorders	1.31 (0.71–2.42)	0.49 (0.12–1.99)	1.03 (0.55–1.92)	1.14 (0.35–3.68)	1.04 (0.60–1.81)
Intelligence disability	0.88 (0.61–1.28)	0.93 (0.63–1.37)	0.89 (0.65–1.21)	0.94 (0.56–1.58)	0.89 (0.68–1.17)
Anxiety disorders	1.10 (0.65–1.87)	0.43 (0.17–1.07)	0.80 (0.48–1.33)	0.90 (0.35–2.30)	0.81 (0.52–1.27)
Unipolar depression	**2.14 (1.14–3.22)**	0.78 (0.46–1.34)	1.28 (0.87–1.90)	1.77 (0.95–2.94)	**1.41 (1.03–1.95)**
Bipolar disorder	0.85 (0.60–1.20)	1.18 (0.89–1.57)	1.04 (0.80–1.34)	1.00 (0.67–1.50)	1.03 (0.83–1.28)
Alcohol use disorder	1.76 (0.55–5.66)	1.91 (0.92–3.94)	**2.21 (1.12–4.36)**	1.50 (0.36–6.32)	**2.00 (1.09–3.70)**
Substance use disorder	**2.33 (1.00–5.44)**	1.72 (0.87–3.40)	**2.06 (1.13–3.73)**	2.20 (0.66–7.32)	**2.01 (1.18–3.42)**

[a]Bold type indicates statistical significance.
[b]Adjusted for demographic data and psychiatric comorbidities.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, ASD = autism spectrum disorder, CI = confidence interval, HR = hazard ratio.

Table 4. Sensitivity Analyses of the Risk of Subsequent Suicide Attempts Among Adolescents and Young Adults With ASD and Controls[a,b]

	Total		≥1 Year[c]		≥3 Year[d]	
	HR	95% CI	HR	95% CI	HR	95% CI
ASD Absence	1	1	1	1	1	1
ASD Presence	**6.07**	**4.64–7.93**	**4.52**	**3.39–6.03**	**3.36**	**2.40–4.70**

[a]Bold type indicates statistical significance.
[b]Adjusted for demographic data and psychiatric comorbidities.
[c]Excluding the first year of observation.
[d]Excluding the first 3 years of observation.
Abbreviations: ASD = autism spectrum disorder, CI = confidence interval, HR = hazard ratio.

CI, 2.86–8.06) with ASD and adolescents (HR = 5.79; 95% CI, 3.98–8.41) and young adults (HR = 5.38; 95% CI, 3.58–8.06) with ASD were more likely to attempt suicide during the follow-up compared with the controls (Table 3). Sensitivity analyses after excluding the first year (HR = 4.52; 95% CI, 3.39–6.03) or first 3 years (HR = 3.36; 95% CI, 2.40–4.70) of observation had consistent findings: ASD was associated with an elevated risk of subsequent suicide attempts in later life (Table 4). Furthermore, unipolar depression (HR = 1.41; 95% CI, 1.03–1.95), alcohol use disorders (HR = 2.00; 95% CI, 1.09–3.70), and substance use disorders (HR = 2.01; 95% CI, 1.18–3.42) were related to an increased risk of suicide attempts (Table 2).

DISCUSSION

Our study results supported the hypothesis that adolescents and young adults with ASD are more likely to attempt suicide in later life compared with those without ASD after adjustment for demographic data and psychiatric comorbidities. ASD was an independent risk factor for attempted suicide regardless of the presence of psychiatric comorbidities, including depression, bipolar disorder, and alcohol and substance use disorders. In addition, ASD patients attempted suicide at a significantly younger age than that of patients without ASD.

Increasing evidence has suggested a potential association between ASD and suicidality in this decade.[4–7,9,10,16–18] As mentioned in the introduction, Cassidy et al reported that 66% of 374 adults with Asperger syndrome had a lifetime experience of suicidal ideation, 35% had a lifetime experience of suicide plans or attempts, and 32% had a history of depression and, furthermore, determined that ASD patients with a history of depression were more prone to reporting suicidal ideation (OR = 4.3; 95% CI, 2.4–7.7) and suicide plans or attempts (OR = 2.4; 95% CI, 1.5–3.8) than were those with no history of depression.[4] Examining the ASD prevalence among 587 adults who attempted suicide, Kato et al[5] showed that 7.3% of them had a diagnosis of ASD and that patients with ASD exhibited greater adjustment problems (70.0% vs 41.5%, $P < .001$) than did patients without ASD. A retrospective study composed of 1,507 adults with ASD revealed that both males (OR = 4.32; 95% CI, 1.93–9.68) and females (OR = 6.68; 95% CI, 2.35–19.02) with ASD displayed an elevated likelihood of having a history of suicide attempts compared with patients without ASD.[16] However, these studies investigating the association between ASD and attempted suicide did not adjust for psychiatric comorbidities, especially mood disorders and alcohol and substance use disorders, in the regression model; thus, whether ASD has an independent impact in the risk of suicidality could not be clarified. In our study, we found that adolescents and young adults with ASD had a greater risk of suicide attempts during the follow-up and had a higher prevalence of suicide-related psychiatric comorbidities, such as depression, bipolar disorder, and alcohol and substance use disorders, compared with those without ASD. Furthermore, the regression model with adjustment for demographic data and psychiatric comorbidities confirmed that ASD was an independent risk factor for attempted suicide regardless of the presence of mood disorders and alcohol and substance use disorders.

Several hypotheses are offered here to explain the significant relationship between ASD and suicidality. First, ASD in adolescence and adulthood may be associated

with mood disorders (depression and bipolar disorder), further increasing the risk of suicidality, including suicidal ideation, suicide plans, and suicide attempts.[4,17,19] In our study, we determined that ASD was an independent risk factor for attempted suicide after adjusting for demographic data and psychiatric comorbidities, such as depression, bipolar disorder, and alcohol and substance use disorders. Second, the core symptoms of ASD, such as deficits in social cognition and communication, restricted thoughts, and cognitive rigidity, may be related to an elevated likelihood of suicidality. Cassidy et al found that patients who planned or attempted suicide had a significantly higher level of self-reported autistic traits than that of patients who did not.[4] Probably because of impairments in social cognition and communication, patients with ASD were more likely to have bullying experiences and social adjustment problems in their lives.[20,21] A recent systematic review study reported that approximately 60% of patients with ASD had an experience of being bullied in school.[21] Holt et al determined that bully victimization was associated with an increased risk of lifetime suicidal ideation (OR = 2.34; 95% CI, 2.03–2.69) and suicidal behaviors (OR = 2.94; 95% CI, 2.36–3.67).[22] In addition, several studies have suggested that both patients with ASD and those who attempted suicide may experience similar difficulties in social processing and social problem solving, such as generating problem solutions and selecting optimal and preferred solutions.[23–25] Third, ASD-related irritability and emotional dysregulation may contribute to the risk of suicidality.[26–28] Increasing evidence has shown that patients with ASD experienced more anger, irritability, and anxiety and less amusement; less frequently used a variety of adaptive emotional regulation strategies (ie, problem solving, cognitive reappraisal); and more frequently used maladaptive strategies (ie, repetitive behavior).[26–28] Previous studies have also shown that patients with suicide attempts exhibited substantial difficulty in regulating their emotions and frequently experienced irritability, agitation, and anxiety symptoms.[29–31] The aforementioned findings collectively indicate that ASD-related emotional dysregulation and maladaptive emotional regulation strategies may increase the risk of suicidality when ASD patients experience depression or social maltreatment.

Several study limitations existed. First, the prevalence of ASD and the incidence of suicide attempts may be underestimated because we included only patients who sought medical help and consultation. However, the diagnosis of ASD and codes of attempted suicide were given by board-certified psychiatrists and physicians, improving the diagnostic validity. Additional clinical studies are required to validate our results. Second, the functioning level of ASD was not available in *ICD-9-CM* system and Taiwan National Health Insurance Research Database. So, we could not evaluate the functioning level of ASD with the risk of attempted suicide. Indeed, some patients with low-functioning autism may exhibit self-harm behaviors occasionally, but their occasional self-harm behaviors were compulsive or stereotypic behaviors with a lack of suicidal ideation or intention and were not regarded as suicidal attempt in our study. Further studies would be necessary to elucidate the relationship between functioning level of ASD and suicide risk. Third, certain information, including the severity of ASD, personal lifestyle, personal life experiences, and family history, is unavailable in the Taiwan National Health Insurance Research Database; therefore, we could not investigate the impacts of these parameters in our study.

In conclusion, adolescents and young adults with ASD had a higher prevalence of suicide-related psychiatric comorbidities, including unipolar depression, bipolar disorder, and alcohol and substance use disorders. Patients with ASD also exhibited an elevated likelihood of attempting suicide in later life compared with those without ASD. ASD was an independent risk factor for subsequent attempted suicide after the adjustment for demographic data and psychiatric comorbidities. In clinical practice, suicide-related symptoms and psychopathology should be more closely monitored among patients with ASD. Additional studies are warranted to elucidate the pathophysiology underlying the association between ASD and suicide and to clarify whether prompt intervention for ASD may reduce this risk.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Suicide section. Please contact Philippe Courtet, MD, PhD, at pcourtet@psychiatrist.com.